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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/211,297	12/14/1998	WILLIAM J. BOYLE	A-451-F	7253

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EXAMINER
DEBERRY, REGINA M

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 03/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/211,297	BOYLE, WILLIAM J.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *20* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continued Prosecution Application

The request filed on 20 December 2002 (Paper No. 19) for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) is acceptable and a CPA has been established.

Status of Application, Amendments and/or Claims

The amendment filed 20 December 2002 (Paper No. 20) has been entered in full. Claims 37-57 were cancelled. New claims 58-81 were added. Claims 58-81 are under examination.

The information disclosure statement filed was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

Matter of Record

Applicant has addressed the rejections of claims 37-57 made under 35 USC 112, first paragraph, scope of enablement and written description set forth in the Advisory Action (17 June 2002, Paper No. 17). Because claims 37-57 were cancelled, the Examiner will address Applicant's argument only if it applies to claims 58-81.

Claim Objections

Claims 64, 69, 75 and 81 objected to under 37 CFR 1.75(c) as being in improper multiple dependent claims. See MPEP § 608.01(n).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 69 and 81 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection. The specification as originally filed does not provide support for the invention as now claimed:

"a composition comprising an antibody or fragment thereof which is present in an amount effective to inhibit bone resorption in a mammal, and a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative and/or adjuvant, wherein the antibody or fragment binds to an epitope of an osteoprotegerin binding protein, the epitope comprising at least part of the amino acid sequence of Figure 4 (SEQ ID NO:39) or Figure 1 (SEQ ID NO:37), the composition further comprising a bone morphogenic factor selected form the group consisting of BMP-1-BMP-12, transforming growth factor-B, a transforming growth factor-B family member, a fibroblast growth factor selected from the group consisting of FGF-1 to FGF-10, an interleukin-1 inhibitor, a TNF a inhibitor, parathyroid hormone, an E series prostaglandin, a bisphosphate, or a bone-enhancing mineral" or

"a composition comprising an antibody or fragment thereof which is present in an amount effective to inhibit bone resorption in a mammal, and a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative and/or adjuvant, wherein

the antibody or fragment binds to an epitope of an osteoprotegerin binding protein and the antibody is produced by immunization with an osteoprotegerin binding protein comprising the amino acid sequence of Figure 4 (SEQ ID NO:39) or Figure 1 (SEQ ID NO:37), the composition further comprising a bone morphogenic factor selected form the group consisting of BMP-1-BMP-12, transforming growth factor-B, a transforming growth factor-B family member, a fibroblast growth factor selected from the group consisting of FGF-1 to FGF-10, an interleukin-1 inhibitor, a TNF a inhibitor, parathyroid hormone, an E series prostaglandin, a bisphosphate, or a bone-enhancing mineral".

Applicant's amendment, filed 20 December 2002 (Paper No. 20), asserts that no new matter has been added and directs support to page 46, lines 7-9 and Example 11 for the written description for the above-mentioned limitations (antibodies binding to epitopes on osteoprotegerin binding protein). However, Applicant does not provide sufficient direction for the written description for the above-mentioned, specifically "*a* ***composition comprising an antibody*** *or fragment thereof* ***AND*** *BMP-1-BMP-12, transforming growth factor-β, a transforming growth factor-β family member, a fibroblast growth factor selected from the group consisting of FGF-1 to FGF-10, an interleukin-1 inhibitor, a TNFα inhibitor, parathyroid hormone, an E series prostaglandin, a bisphosphate, or a bone-enhancing mineral".*

The exact wording or connotation of the instant claims is not readily apparent from said sections. The specification as filed does not provide a written description or set forth the metes and bounds of this "limitations". The instant claims now recite

limitations which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as-filed.

Applicant is required to cancel the new matter in the response to this Office action. Alternatively, Applicant is invited to provide specific written support for the "composition comprising an antibody or fragment thereof and BMP-1 to BMP-12...." indicated above or rely upon the limitations set forth in the specification as filed.

Claims 64 and 75 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to the composition of claim 63 and 74 (respectively) prepared by the steps of immunizing a transgenic animal capable of producing human antibodies and recovering human antibodies.

The instant claims are not supported by an enabling disclosure. The specification fails to teach how to make the instant invention without undue experimentation. The specification does not teach how to make a transgenic animal. The specification does not disclose what types of animals are good candidates for transgenes. The specification fails to teach the steps for making human antibodies by immunizing a transgenic animal. The specification fails to teach how one would determine if the transgenic animal is carrying the gene. The specification does not disclose working examples. Applicant has provided little or no guidance to enable one of ordinary skill in

the art to make the composition, without undue experimentation. The art of making transgenic animals and transgenic animals which are capable of producing heterologous antibodies is extremely complex and unpredictable. Please see Jakobovits, Curr. Opin. Biotech., 1995 and Bruggemann *et al.*, Immunol. Today, 1996. One skilled in the art cannot readily anticipate the results of these types of experiments. Furthermore, the quantity of experimentation needed is significant and definitely not routine.

Due to the large quantity of experimentation necessary to make the transgenic animal, to screen the animal for the transgene, to immunize the transgenic animal and generate human antibodies, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention and the state of the prior art which establishes the unpredictability of making transgenic animals, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 58, 60, 70, 72 are rejected under 35 U.S.C. 102(e) as being anticipated by Anderson *et al.*, US Patent No. 6,419,929 B1.

The instant claims are drawn to a composition comprising an antibody or fragment thereof which is present in an amount effective to inhibit bone resorption in a mammal, and a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative and/or adjuvant, wherein the antibody or fragment binds to an epitope of an osteoprotegerin binding protein, the epitope comprising at least part of the amino acid sequence of Figure 4 (SEQ ID NO:39).

Anderson teaches the polynucleotide sequence of human RANKL (receptor activator of NF-kB ligand) (column 4, lines 5-15). Anderson teaches the amino acid sequence of human RANKL (column 4, lines 32-53). Anderson teaches the different domains of RANKL (column 2, lines 9-20). The human RANKL protein (SEQ ID NO:13) of Anderson is 100% identical to SEQ ID NO:39 (please see sequence query, Appendix A; Anderson reference, column 21, line 25-column 22, line 5; columns 63-66 and claims). Because Anderson teaches the exact polypeptide sequence, the protein of Anderson is expected to have the activity of inhibiting bone resorption in a mammal. A

compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

Anderson teaches the use of RANKL proteins to make antibodies (column 9, lines 56-64). Anderson teaches pharmaceutical compositions comprising RANKL antibodies. RANKL and agonistic antibodies will be useful in protecting RANK-expressing cells from the negative effects of chemotherapy or the presence of high levels of TNF-α such as occur in sepsis (column 15, lines 28-38 and lines 61-67) (claim 58). Anderson teaches the preparation of monoclonal antibodies against RANKL. Rodents are immunized with RANKL (column 22, line 30-column 23, line 25) (claims 60, 70, 72).

Claims 59, 60, 71, 72 are rejected under 35 U.S.C. 102(e) as being anticipated by Gorman *et al.*, US Patent No. 6,242,586 B1.

The instant claims are drawn to a composition comprising an antibody or fragment thereof which is present in an amount effective to inhibit bone resorption in a mammal, and a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative and/or adjuvant, wherein the antibody or fragment binds to an epitope of an osteoprotegerin binding protein, the epitope comprising at least part of the amino acid sequence of Figure 1 (SEQ ID NO:37).

Gorman teaches the polynucleotide and polypeptide sequence of mouse 499E9 (columns 5-6 and Table 1). Gorman teaches the different domains of 499E9 (column 6, lines 1-9). The mouse 499E9 protein (SEQ ID NO:2) of Gorman is 100% identical to

SEQ ID NO:37 (please see sequence query, Appendix B; Gorman reference, Table 1; column 9, line 60-column 10, line 17 and claims). Because Gorman teaches the exact polypeptide sequence, the protein of Gorman is expected to have the activity of inhibiting bone resorption in a mammal. A compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

Gorman teaches that synthetic peptides or purified proteins of 499E9 are presented to an immune system to generate monoclonal antibodies (column 27, line 64-column 28, line 9), Gorman teaches administration of 499E9 antibodies in pharmaceutically acceptable carriers (column 21, lines 32-43) (claims 59, 60, 71, 72).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 62, 63, 65-68, 73, 74, 77-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson *et al.*, US Patent No. 6,419,929 B1 in view of Gorman *et al.*, US Patent No. 6,242,586 B1. The teachings of Anderson and Gorman are described above. The references do not teach a composition wherein the antibody or fragment thereof binds to a specific epitope on SEQ ID NO:37 or SEQ ID NO:39 (claims 65-68, 77-80); chimeric (claims 62, 73) or human antibodies (claims 63, 74). The references, however, would motivate one skilled in the art to make them.

One skilled in the art could make antibodies which bind different areas of SEQ ID NO:39, because Anderson teaches a protein sequence (RANKL) which is 100% identical to SEQ ID NO:39 and teaches the domains of RANKL (column 2, lines 5-32). Anderson states how to make antibodies against RANKL which could be agonistic antibodies or antagonistic/blocking antibodies (column 15, lines 61-67 and column 23, lines 20-25).

One skilled in the art could make antibodies which bind different areas of SEQ ID NO:37, because Gorman teaches a protein sequence (499E9) which is 100% identical to SEQ ID NO:37 and teaches the domains of 499E9 (column 5-6). Gorman states that 499E9 would be useful for raising antibodies to linear and conformational epitopes (column 4, line 66-column 5, line 3). Gorman states that it is desirable to prepare monoclonal antibodies from human host (human antibodies)(column 15, lines 65-66). Gorman suggests the therapeutical uses of blocking antibodies made against 499E9 (column 21, lines 43-56). Gorman discloses that antibodies may be used with modifications such as chimeric and humanized antibodies (column 16, lines 16-19).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the instant invention of a composition comprising an antibody or fragment thereof which binds to specific epitopes of SEQ ID NO:37 or SEQ ID NO:39 and a pharmaceutically acceptable diluent. The motivation and expected success is provided by Anderson and Gorman who suggest the use of antibodies, made against the protein, as agonist or antagonists to elicit a biological response *in vivo*.

Claim 76 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gorman *et al.*, US Patent No. 6,242,586 B1 in view of Cabilly *et al.*, US Patent No. 4,816,567.

The teachings of Gorman *et al.* are described above in the 102(e) rejection. Gorman does not teach a composition comprising an antibody or fragment thereof wherein the antibody or fragment is produced by expression of a nucleic acid encoding the antibody or fragment in transformed or transfected host cell.

Cabilly teaches a method of producing antibodies by recombinant techniques (column 4, lines 19-54, column 8, lines 21-61). Cabilly teaches the cloning of the nucleic acid of the antibody into a vector and the transformation of the vector into host cells (column 11, line 58-column 12, line 68).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the inventions of Gorman and Cabilly to make the instant invention of a composition comprising an antibody which recognizes SEQ ID NO:37 wherein the antibody is made by recombinant techniques. The motivation and expected success is provided by Gorman who teaches a sequence which is 100% identical to SEQ ID NO:37 and Cabilly who teaches recombinant immunoglobulin preparations. In addition, Cabilly teaches that antibody recombinant techniques provides the advantages of constructing chimeric and other modified forms of antibodies.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on 9:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RMD
March 21, 2003

GARY KUNZ
SUPERVISORY PATENT EXAMINER
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